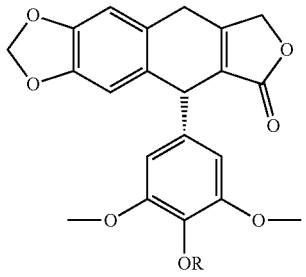
NOVEL DERIVATIVE OF BETA-APOPICROPODOPHYLLIN AND METHOD OF PREPARING THEREOF

TECHNICAL FIELD

[0001] The present invention relates to a novel derivative of 3-apopicropodophyllin and a method of preparing the same, and more particularly, a compound represented by Formula 1 below, which is a novel derivative of β-apopicropodophyllin derived from podophyllotoxin, which is an anticancer agent, a method of preparing the same, and a composition for treating cancer, which includes the compound.

[Formula 1]

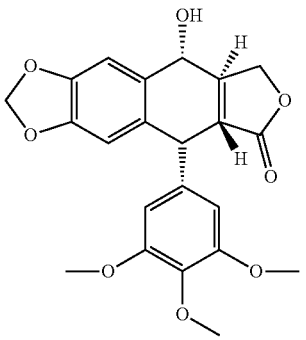


[0002] In Formula 1, R is a C_2 to C_{10} alkyl group, a C_2 to C_{10} alkyl group containing an allyl- or alkyne, a —$[CH_2]_n$—C_3 to C_8 cycloalkyl group, a substituted or unsubstituted —$[CH_2]_n$-phenyl group, a substituted or unsubstituted —$[CH_2]_n$—C_5 to C_6 heteroaromatic group, a —C(=O)—C_1 to C_8 alkyl group, a substituted or unsubstituted —C(=O)—$[CH_2]_n$-phenyl group, or a substituted or unsubstituted —C(=O)—$[CH_2]_n$—C_5 to C_6 heteroaromatic group, wherein n is an integer of 0 to 6.

BACKGROUND ART

[0003] Podophyllotoxins has been used as therapeutics for more than 1,000 years. In the 1960s, Sandoz Limited synthesized derivatives of podophyllotoxin, below Formula A. Semi-synthetic derivatives of podophyllotoxin, etoposide and teniposide were obtained in 1966 and 1967, respectively. In 1987, etoposide got US FDA approval as an antineoplastic drug. Teniposide got US FDA approval for clinical use for several types of cancer, lung, leukemia and so on in 1993. Both two anti-cancer agents have been used single, combination therapy with other anticancer agents.

[Formula A]

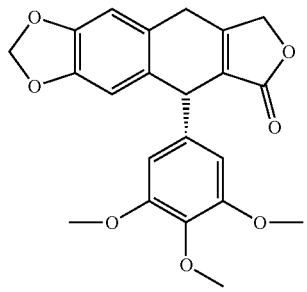


[0004] Mode of action of podophyllotoxin, etoposide, teniposide and other podophyllotoxin derivatives as an anticancer agent had been published DNA topoisomerase II inhibition (J. C. Wang, J. Biol. Chem., 1991, 266(11), 6659-62). Although etoposide and teniposide have been showed good clinical effect in cancer patients, they have limitation for long term treatment as toxicity. The discovery and developing research for new drug to overcome the shortcoming has been continued.

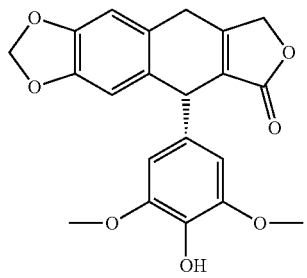
[0005] Bristol-Myers Squibb Co. in US and Microbial Chemistry Research Foundation in Japan issued patent GB 2,207,674 A (Feb. 8, 1989) and EP 0,196,618 A1 (Oct. 8, 1986), respectively. And Adla Mallareddy, et al. in India suggested 4-Aza-2,3-didehydropotophyllotoxin derivatives and anticancer effect WO 2012/076942 A1 (Jun. 14, 2012) and also Kim, Song-Bae in S. Korea did 4'-demethy-4'-O-substituted-1-deoxypodophyllotoxin derivatives and anticancer effect (WO 2002/040489 A1 (May 5, 2002).

[0006] β-Apopicropodophyllin of below Formula B and 4'-demethyl-β-apopicropodophyllin of below Formula C were obtained and identified by halogenation and followed by pyrolysis from podophyllotoxin, and demethylation of β-apopicropodophyllin, respectively (Journal of the American Chemical Society, 1954, 76, 1182-1185).

[Formula B]



[Formula C]



[0007] Anti-cancer effect of β-apopicropodophyllin (Formula B) in detail was published in 2018 [Toxicology and Applied Pharmacology, 2018, 357, 39-49 and patent KP 10-2090554 B1 (Mar. 12, 2020)]. While, in 1986, Anticancer effect and inhibition of human DNA-topoisomerase II were not reported in detail (Journal of Medicinal Chemistry, 1986, 29, 1547-1550).

PRIOR ART DOCUMENTS

Patent Document

[0008] EP 0,196,618 A1 (Oct. 8, 1986)
[0009] GB 2,207,674 A1 (Feb. 8, 1989)
[0010] WO 2002/040489 A1 (May 23, 2002)